

CURRENT TOPICS

Immunisation of infants against *Haemophilus influenzae* type b in the UK

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Haemophilus influenzae is one of the micro-organisms that make up the commensal flora of the upper respiratory tract. Carriage is common, but compatible with good health. None the less, *H influenzae* is a pathogen and, in the case of encapsulated type b organisms, causes life threatening, invasive (bacteraemic) infections, the most common and serious being meningitis and epiglottitis (table 1).¹ The type b capsule is a crucial virulence factor and is composed of polyribosyl ribitol phosphate (PRP).² Serum antibodies to the type b capsule can protect against invasive disease but immunocompetence generally takes some years to mature.³⁻⁵ Young children are therefore particularly susceptible to *H influenzae* type b and its potential to disseminate through the bloodstream (70% of cases occur in infants less than 2 years old).⁶ During the past two decades intensive efforts have been made to develop a vaccine that could hasten the onset of protective immunity with the goal of eliminating most serious *H influenzae* type b infections. There has been spectacular progress and this seems an opportune time to summarise the future of *H influenzae* type b immunisation in the UK.⁷

The crucial science that has been applied to developing effective vaccines against *H influenzae* type b for use in infants stems from observations made more than 60 years ago.⁸ Purified polysaccharides, such as PRP, are poor immunogens when used in their natural state and especially in children less than 2 years old.³ By linking the polysaccharide PRP chemically to a protein carrier, however, a conjugate

vaccine is produced that can provoke a serum antibody response to the polysaccharide, which is sufficient to protect against disease. Importantly, this response displays immunological memory—that is, it has a boosting effect when there is re-exposure to the relevant antigen. Four *H influenzae* type b conjugate vaccines have so far been developed (table 2),⁹ and each has been evaluated in clinical trials. Infants in these studies received either two or three doses of conjugate vaccine by intramuscular injection between the ages of 2 and 6 months. Comparison of data obtained for the different lots of any one vaccine (for example, PRP-D) in different studies or for the different vaccines (even in the same country) are not valid because of many uncontrolled variables (for example, population immunised, number of doses of vaccine, antibody assay used, and so on). In all cases the conjugate vaccines resulted in significantly higher titres of total serum antibody to type b capsule than would have been expected in infants who had not been immunised. In general, a level of >0.15 µg/ml correlates with protection in the short term.

Although it is too early to judge conclusively the relative merits of these vaccines, all four seem to be suitable for use in infants. Important and unequivocal variations in immunogenicity have, however, been shown, and it is likely that these differences will correlate with each vaccine's relative ability to prevent disease.¹⁰

Is a vaccine against *H influenzae* type b needed in the UK?

Epidemiological data from regional surveys of microbiologically confirmed infection have shown that the probability of a child contracting invasive *H influenzae* type b disease in the UK by the age of 5 is about 1:600, and the probability of it being *H influenzae* type b meningitis

Table 1 Carriage and pathogenicity of *H influenzae*

Strains of <i>H influenzae</i>	Common rates of upper respiratory tract carriage	Principal signs of pathogenicity
Non-encapsulated	50-80%	Exacerbations of chronic bronchitis, otitis media, sinusitis, and conjunctivitis; patients commonly adults; bacteraemic infections rare but may occur in neonates
Encapsulated type b	2-4%	Meningitis, epiglottitis, pneumonia and empyema, septic arthritis, cellulitis, osteomyelitis, pericarditis, bacteraemia; rarer signs include glossitis, tenosynovitis, peritonitis, endocarditis, and ventriculitis, associated with infected shunt tubing
Encapsulated types a, c, d, e, and f	1-2%	Rarely incriminated as pathogens

Adapted from Turk with permission.¹

Table 2 Immunogenicity of *H influenzae* type b conjugate vaccines

Vaccine and manufacturer	No of infants immunised	Country	Geometric mean titre of serum antibodies to type b capsule (µg/ml)*
PRP-D (Connaught Laboratories)	64	USA	0.53
	72	Finland	0.63
PRP-T (Pasteur-Merieux)	117	France	4.80
	81	Chile	11.32
PRP-OMP (Merck, Sharp and Dohme)	475	USA	4.63
HbOC (Lederle-Praxis)	163	USA	16.84
	46	Finland	4.37

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*Measured by radioimmunoassay at about 7 months.

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is 1:850⁶ (AJ Howard, personal communication). There are about 65 deaths each year.⁶ Comparative rates for representative European countries, and states in North America and Australia indicate that the problem of *H influenzae* type b meningitis in the UK is similar to that reported elsewhere in the western world (table 3).⁷

Few reliable data are available about morbidity, especially concerning the apparently permanent effects on the central nervous system that have been reported elsewhere in children who have survived episodes of *H influenzae* type b meningitis.¹¹ Devastating damage to the central nervous system occurs in a minority, but sensorineural hearing deficits are likely to be a problem in about 6% of children who recover from *H influenzae* type b meningitis.¹² It is likely that many undetected, or unreported, neurological deficits occur (for example, motor incoordination, deficit in intelligence, or learning difficulties) as a result of *H influenzae* type b meningitis, but there have so far been no prospective studies published for the UK. Overall, the impact of *H influenzae* type b infection, especially meningitis, seems to be comparable with that of poliomyelitis before the introduction of routine immunisation.¹⁰ Polio occurred in epidemics, however, and young adults were particularly prone to serious disease. These patterns of disease are more analogous to infections with meningococci, which have attracted much attention from the media in recent years and resulted in considerable anxiety in affected communities. Because *H influenzae* type b infections occur sporadically, this may explain in part why they have attracted less attention than would seem merited. In every year since 1982 (when the Office of Population Censuses and Surveys began reporting cases of both meningococcal and *H influenzae* type b meningitis) the incidence of *H influenzae* type b meningitis in children in the UK has been greater than that of meningococcal meningitis.¹³

Additional concerns are that there has been an absolute increase in the incidence of *H influenzae* type b infection in the UK over the past decade,¹³ and primary resistance to antibiotics may lessen the effectiveness of treatment. About 11% of isolates of *H influenzae* type b are now resistant to ampicillin (there was none before 1974) and rare instances of resistance to chloramphenicol have been reported.¹⁴

There is, therefore, a compelling case for routine immunisation against *H influenzae* type

b infection providing that the proposed vaccine is safe, highly effective, compatible with our existing routine immunisation programme, and not prohibitively expensive.

Are vaccines against *H influenzae* type b safe?

Extensive investigations have shown that the four vaccines are tolerated well and serious adverse effects do not occur.^{10 15} *H influenzae* type b conjugate vaccines are already used routinely for infants in the USA, Finland, Iceland, and Germany. It can be concluded with confidence that *H influenzae* type b conjugate vaccines are among the safest bacterial vaccines ever proposed for routine use. It should be anticipated, however, that serious illnesses or unexpected deaths (for example, cot deaths) may occur that are temporally related to, but not caused by, immunisation.

Are vaccines effective against *H influenzae* type b?

Trials have established that vaccines against *H influenzae* type b are immunogenic at all ages from 2 months or older.^{9 10} There are several important variables which affect the immune response, however, and these include: age at which the primary series of two or three immunisations is given, interval between each dose of vaccine, and the choice of conjugate.¹⁰ The immune response may also be influenced by genetic factors.¹⁶ In general, PRP-D has proved to be the least immunogenic in infants; PRP-OMP and, to a lesser extent, PRP-T stimulate a substantial antibody response after the first dose, whereas HbOC and PRP-D do so only after the second dose. The response to booster doses is least strong for PRP-OMP.

Although these comparisons of immunogenicity are helpful as indicators of the potential of each vaccine, the important criterion is the extent to which vaccines against *H influenzae* type b prevent disease. Efficacy studies have shown that PRP-D, HbOC, and PRP-OMP can prevent more than 90% of *H influenzae* type b disease.^{5 7 15} A formal efficacy study of PRP-T has not been completed, but this vaccine is currently offered as a routine vaccine to all children in Finland, and its efficacy is also being evaluated in the UK. PRP-D proved to be ineffective in preventing *H influenzae* type b disease in a trial of its efficacy among Alaskan children.¹⁷ Its relatively lower immunogenicity, combined with certain epidemiological characteristics of *H influenzae* type b disease in Alaska, make it likely that this disappointing result could be reversed by the choice of a different conjugate—a possibility that is supported by the excellent results obtained with PRP-OMP among native American Indians in Arizona.¹⁵

Is immunisation with *H influenzae* type b conjugate vaccine compatible with the existing routine immunisation schedule?

Extensive studies elsewhere have documented the feasibility of giving vaccine against *H*

Table 3 Incidence of *H influenzae* type b meningitis in developed countries

Country	Yearly incidence of <i>H influenzae</i> type b meningitis/100 000 children aged <5 years
USA: Texas, Minnesota, California, North Carolina, and Maryland	19–67
Finland	26
Netherlands	22
Sweden	31
UK	24
Australia: Victoria and New South Wales	20–25

Modified from Vaccine with permission.⁷

influenzae type b at the same time as the routine immunisations against diphtheria, pertussis, tetanus (DPT), and polio.⁵ Given the recent modifications to the UK schedule,¹⁸ it is important to study carefully the use of vaccines against *H influenzae* type b that are given at 2, 3, and 4 months because other studies (excluding one recent one) have not precisely duplicated this schedule. Preliminary results suggest that responses of children in the UK using the accelerated schedule are excellent and further studies should expand on these data during the next few months.¹⁹ It is also possible that vaccine against *H influenzae* type b could be given in the same syringe mixed with DPT rather than as a separate injection—a sensible innovation that could potentially further increase the acceptability of the vaccine, and make routine immunisation against *H influenzae* type b more convenient to give. The issue of the possible need for booster doses will also require some investigation, but there are insufficient data at present about the duration of protection after immunisation of young infants.

How will it be known whether *H influenzae* type b conjugate vaccines are acceptable and effective?

Relevant to both questions will be the accurate documentation of vaccine uptake. No vaccine can be successful if it does not reach the target population. Thus the much needed improvements in our current routine immunisation programme that have occurred recently, and the improved monitoring of uptake of vaccination, are important tools for evaluating the success of the introduction of *H influenzae* type b vaccination. Systematic reporting of episodes of invasive (bacteraemic) *H influenzae* type b infections may be based upon the current Communicable Disease Surveillance Centre laboratory reporting system. There is, however, a recent initiative through the Public Health Laboratory Service (PHLS) to provide more detailed prospective data on the incidence of *H influenzae* type b infection in six regions of England and Wales. Scotland has maintained an independent and relatively complete system for recording invasive *H influenzae* type b infections. It should therefore be possible to gauge the impact of routine *H influenzae* type b immunisation by monitoring the incidence of disease and relating these data to our past experience.

Despite obvious weaknesses, this approach to assessing the effectiveness of vaccination is probably the only practical option in the UK. Placebo controlled studies are no longer ethical. Prospectively designed efficacy trials are difficult to organise and their cost can be prohibitive.⁷ (A prospective open implementation study of PRP-T vaccine involving sequential introduction of vaccine at a district level is underway in the Oxford region in anticipation of the national introduction of *H influenzae* type b immunisation, which will be late in 1992.) Given primary efficacy data on three of the four *H influenzae* type b conjugate vaccines, and implementation studies on the fourth

(PRP-T),* it seems sensible to invest in a prospective registry of cases of *H influenzae* type b infection in both immunised and unimmunised children, which could then be analysed in a case control manner. For this, it will be essential to ensure that episodes of *H influenzae* type b disease are fully documented and that the disease isolates are verified at an appropriate PHLS reference laboratory.†

Conclusion

The successful development of *H influenzae* type b conjugate vaccines is a milestone in the control of microbial diseases. The achievement is especially noteworthy in that these conjugate vaccines elicit in infants specific immune responses that are greater than those achieved by natural exposure to *H influenzae* type b (or cross reactive bacteria) irrespective of whether asymptomatic carriage or invasive disease resulted from the natural exposure. Because the immune response of infants to native capsular polysaccharides is often too slight to result in protection, the exploitation of the hapten carrier principle to formulate conjugate vaccines opens the door for development of other conjugate polysaccharide vaccines for the prevention of bacterial meningitis and invasive infections caused by encapsulated bacteria such as pneumococci, meningococci, coliforms, and group B streptococci. Finally, *H influenzae* type b disease is a global problem, so the successful implementation of conjugate vaccines in industrialised countries can pave the way for their use in developing countries.

*Clinical experience with 70 000 children immunised has shown no cases of infection after either two or three doses of a three dose primary schedule (B Fritzell, personal communication).

†The recognised PHLS reference laboratory for *haemophilus* is at the John Radcliffe Hospital, Oxford.

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